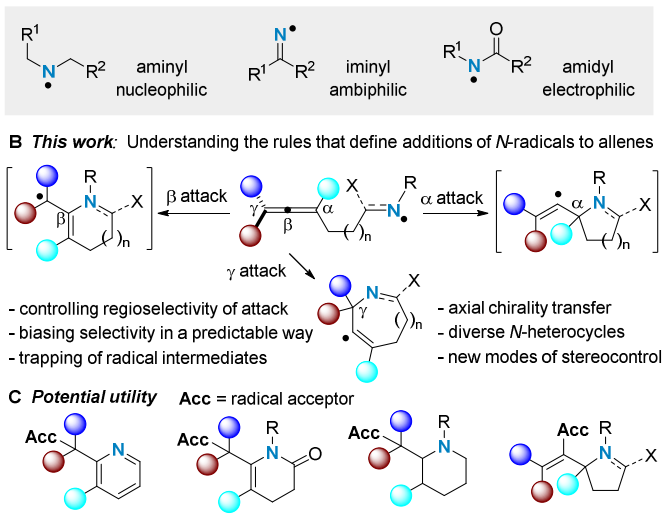
Strategies for Aldoxime and Ketoxime Umpolung: Versatile Syntheses of Amines and Heterocycles

Our initial efforts to generate *N*- and *C*-centered radicals from oximes under photochemical conditions were not successful. To better understand the chemistry of *N*-centered radicals, we turned our attention to achieving the versatile syntheses of amines and heterocycles using a modified strategy. While the additions to *N*-radicals to alkenes and alkynes have been well-studied, it is surprising that the analogous regio- and stereocontrolled additions to allenes are underdeveloped, despite the potential for efficient construction of *N*-heterocycles in pharmaceuticals, agrochemicals, and natural products. Other attractive features of the amination or amidation of allene precursors include: 1) three sites for tunable amidation are available through the judicious choice of allene/radical source/catalyst, 2) there is potential for transfer of axial-to-point chirality to secure enantioenriched amines, and 3) trapping of vinyl or allyl radical intermediates with acceptors other than conventional hydrogen-atom donors to diversify the products that can obtained from the chemistry.

Scheme 1. Site-selective attack of *N*-radicals on allenes.



Nitrogen-centered radicals come in a variety of 'flavors', with their reactivities broadly categorized as nucleophilic, electrophilic, or ambiphilic (Scheme 1A). Students working on this project have benefited from opportunities to design experiments and computational studies to understand how the allene substitution pattern, the tether length between the nitrogen source and the allene, the electronic features of the *N*-radical, and the reaction conditions can be harnessed to develop synthetic approaches to valuable heterocycles (Scheme 1C) that are complementary to transition metal and ionic-based protocols. As the 'rules' for tuning the selectivity of *N*-centered radical additions to allenes are not well-established (Scheme 1B) and differ from those described for radical additions to alkenes, students have the chance to inform the chemical community about new patterns of reactivity in this growing research area.

General approaches to install all three types of *N*-centered radicals (Scheme 2) into allenes were developed; in addition to the type of radical precursor, the tether length and the allene substitution pattern are easily varied. Inspired by reports by Leonori, aryloxyamide **1a** was prepared and subjected to visible light irradiation (Table 1). Reaction of **1a** in acetone using a 13 W green LED in the presence of an Eosin Y photocatalyst, K_2CO_3, and 1,4-cyclohexadiene (CHD) as the H-atom donor, furnished 41% of the 5-*exo*-trig cyclization product after 21 h (entry 1). To our surprise, 18% of **1b** was observed in the absence of Eosin Y (entry 2). While the UV-vis spectrum of **1a** indicated a λ_{max} <350 nm, the fact that irradiation with green LED and CFL yielded cyclization product prompted us to try other light sources. Optimal conditions (entry 4) gave 78% of **1b** after 1.5 h. CHD could be replaced with other H-atom donors, including 9,10-dihydroanthracene and Hantzsch ester (entries 5-6). Cyclization does not proceed in the absence of light or K_2CO_3 (entries 7-8). Carrying out the chemistry in *d*-acetone in the absence of 1,4-CHD (entry 9) gave 49% **1b**, with 37% D-incorpor-ation from solvent. Addition of 1.5 equivalents of TEMPO (entry 10) decreased the overall yield to 21%, suggesting a radical mechanism is operative. As expected, removing both CHD and K_2CO_3 from the mixture (entry 11) resulted in no reaction to **1b**.

Scheme 2. Installation of *N*-radical sources.

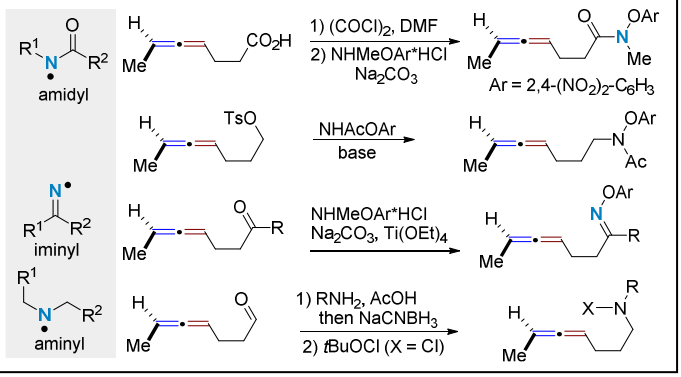
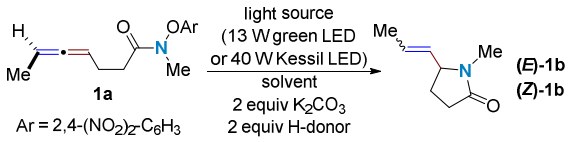


Table 1. Optimization of amidyl radical addition to allenes.



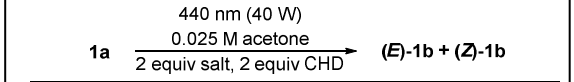
entry	source	solvent (M)	H-donor	time (h)	yield[a] (*E*:*Z*)
1[b]	green LED	acetone (0.1)	1,4-CHD	21	41% (2.1:1)
2	green LED	acetone (0.1)	1,4-CHD	21	18% (2.2:1)
3	440 nm	acetone (0.1)	1,4-CHD	5	76% (2.2:1)
4	**440 nm**	**acetone (0.025)**	**1,4-CHD**	**1.5**	**78% (2.1:1)**
5	440 nm	acetone (0.025)	9,10-DHA	4	71% (2:1)
6	440 nm	acetone (0.025)	Hantzsch ester	1	74% (2.3:1)
7	no light	acetone (0.025)	1,4-CHD	1.5	0%
8	440 nm	acetone (0.025)	1,4-CHD, no base	24	0%
9[c]	440 nm	acetone (0.025)	none	24	49% (2:1)[d]
10	440 nm	acetone (0.025)	1,4-CHD, TEMPO	1.5	21% (2.1:1)
11	400 nm	acetone (0.025)	none, no base	16	0%

[a]NMR yield of *E*:*Z* isomers with 1,3,5-trimethoxybenzene as internal standard; [b]2 mol% of Eosin Y; [c]*d*-acetone solvent; [d]3:1 D:H ratio.

Eosin Y is not required for successful radical cyclization, but K_2CO_3 is critical. Insight into the role of base was carried out by varying both the anion and cation of the salt (Table 2). KCl (entry 1) showed lower

reactivity and yield, while $KHCO_3$, KOAc, KOH, and Cs_2CO_3 (entries 2-5) were similar to K_2CO_3, albeit displaying prolonged reaction times. The lack of a clear trend between the basicity of the salt and yield and/or reaction time argues against its role solely as a Brønsted base; no change in the UV-Vis spectrum of **1a** following addition of K_2CO_3 argues against formation of an electron donor-acceptor (EDA) complex that undergoes irradiation at the charge-transfer band. Comparing K_2CO_3 to Cs (entry 5), Na (entry 6) and Li (entry 7) carbonates gave similar results, with the exception of Na_2CO_3. The higher solubility of Cs_2CO_3 (entry 5) cut reaction time in half as compared to K_2CO_3; Bu_4NOAc (entry 8) performed similarly. Finally, reducing the amount of K_2CO_3 to 0.2 equivalents still gave 83% yield of **1b** after 5.6 h. Taken together, these results support the role of the salts as simple electrolytes, where irradiation at 440 nm is sufficient to directly excite **1a** to promote either direct homolysis of the N-O bond or a SET event that initiates formation of the amidyl radical.

Table 2. Impact of salts on the reaction.



entry	salt	time h	yield[a] (E:Z)	entry	salt	time h	yield[a] (E:Z)
1	KCl	25	62% (2:1)	6	Na_2CO_3	5	32% (2.3:1)
2	$KHCO_3$	9	76% (2.2:1)	7	Li_2CO_3	3	60% (2.1:1)
3	KOAc	2	73% (2.3:1)	8[b]	TBA(OAc)	2	65% (2.2:1)
4	KOH	5	77% (2.2:1)	9[c]	K_2CO_3	5.6	83% (2.3:1)
5	Cs_2CO_3	0.8	72% (2.3:1)				

[a]NMR yield with 1,3,5-trimethoxybenzene as internal standard; [b]14% **1a** remaining; [c]0.2 equivalents of K_2CO_3

Studies to investigate the scope of this chemistry are still in progress (Table 3), but several additional substrates have already been prepared and will soon be subjected to photocyclization. With n = 1, the expected product is **2b**; however, when n = 2, the lactams **3b** and **5b** are formed in good yields. Other substrates that contain a three-atom tether between N and the allene were also investigated; 5-*exo*-trig cyclization in trisubstituted allenes is expected to be favored over the competing 6-*endo*-*dig* cyclization to yield **6-7b**, due to stereoelectronic prerequisites for a radical attack on a π bond. We will also explore whether radical stabilizing groups, such as Ph, other aryl groups, and electron-withdrawing groups, including -CO_2Et and –CN, will retard 5-*exo* attack and accelerate the 6-*endo* cyclization to furnish the desired six-membered heterocycles **9-11b**. Finally, when n = 3 (four atom tether between the α allene carbon and the nitrogen), we found that **12a** cyclizes smoothly to give 6-*exo*-trig product **12b** in good yield, with no apparent competing H-atom abstraction.

One of our future goals is to compare the behavior of other types of *N*-centered radicals to amidyl radicals in additions to allenes. For example, we are curious how the ambiphilic behavior of iminyl radicals may be manipulated in combination with allenes of varying substitution patterns and electronics to secure access to valuable *N*-heterocycles, including pyrrolines, pyrroles, 2-azadienes, and pyridines (Scheme 3). Experiments to explore the potential for axial-to-point chirality transfer will also be undertaken. New strategies for the generation of 'nucleophilic' aminyl radicals will be developed and their behavior in regiodivergent additions to allenes studied for heterocycle synthesis. To our knowledge, the reactivity of these types of radicals to allenes has not been reported.

Another important future goal is to develop methods to trap the radical intermediates that arise from additions of *N*-centered radicals to allenes. Thus far, in addition to successful trapping of vinyl radical intermediates with cyclohexadiene and other hydrogen atom donors, we have successfully utilized $P(OR)_3$ to give α-aminated vinyl phosphonates. Other potential acceptors we will investigate include α,β-unsaturated carbonyls, electron-rich aromatics, halogens, and oxygenated radical traps. In the former example, trapping of a vinyl radical with oxygen will generate an enol ether that may add to another electrophile; in this manner, a radical cascade that functionalizes all three unsaturated allene carbons in a single pot can be envisaged. Computational studies will be carried out to better understand and predict reactivity patterns in this chemistry.

Scheme 3. Addition of imidyl radicals to allenes.

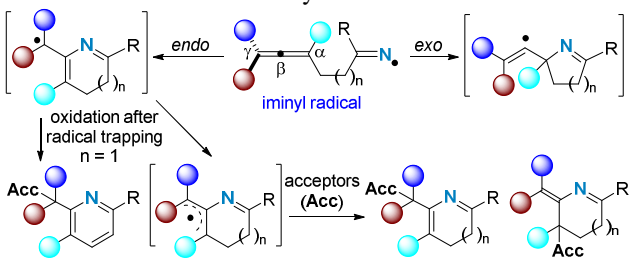
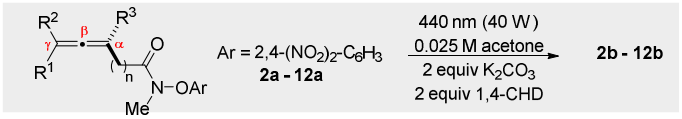


Table 3. Scope: Addition of amidyl radicals to allenes.



major product or substrate		yield (E:Z)[a]	major product or substrate	yield (E:Z)[a]
n = 1	**2b**	in progress		
n = 2	**3b** (R = *i*Pr)	86% (2.1:1)	**9b**	in progress
	4b (R = Ph)	in progress	**10b**	in progress
	5b (R = H)	65%		
	6b	62% (1:1)	**11b**	in progress
	7b	in progress		
	8b[c]	64% (2.7:1)	**12b**[b]	67% (2.2:1)

[a]E:Z ratio was determined based on crude ^{1}H NMR. [b]H-atom abstraction product, 6%. [c]H-atom abstraction product, 16%.

Students involved in this research have gained experience in standard experimental techniques for handling both air-stable and air-sensitive organic compounds, been introduced to the principles underlying visible-light photochemistry and photocatalysis, learned to measure reaction kinetics using various spectroscopic techniques, and carry out computational modeling of species with unpaired electrons.